REMARKS

This Amendment and Response is in reply to the final Office Action dated June 23, 2008. A one (1) month Petition for Extension of Time is filed concurrently herewith. Therefore the period for timely response extends up to and including October 23, 2008.

Claims 19 – 31 are pending. Applicants have canceled claims 7 – 18 without prejudice or disclaimer. Claims 19 – 31 are new claims that have been added. Support for the new claims can be found at least in the original claims and at page 6, line 12 to page 7, line 26. No new matter has been added. Applicants wish to thank the Examiner for careful review and consideration of the present application.

Preliminary Matters

Applicants wish to thank the Examiner for withdrawal of the rejections under 35 U.S.C. § 101 and withdrawal of rejections under 35 U.S.C. § 112 set forth in the previous Office Action.

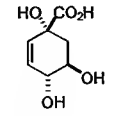
Claim Rejections under 35 U.S.C. § 102

Claims 1 and 6 are finally rejected under 35 U.S.C. 102(b) as being anticipated by Frederickson et al. (Journal of Organic Chemistry, 1999, 64 pages 2612 – 2613).

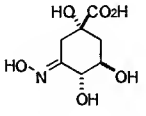
Claims 1 and 6 have been canceled, without disclaimer or prejudice. New claims 19-31 recite R^1 or R^2 groups not found in the structures of the cited art. Therefore the claim rejections under 35 U.S.C. § 102 are moot. Applicants respectfully request withdrawal of the rejections under § 102. Applicants further assert that, for example, R^2 substituents of the amended claims are not obvious over the substituents in the recited art (Frederickson et al.; e.g. hydrogen and oxime) in that the R^2 substituents have different chemical structures and therefore offer improved levels of inhibition of dehydroquinase enzymes as described below.

The art discloses inhibitors of type II dehydroquinases. Frederickson et al. (Journal of Organic Chemistry) discloses compounds **10** and **19** as competitive inhibitors of *M. tuberculosis*

type II dehydroquinase, with values of Ki of 200 μM and 20 μM, respectively.



6 (200 μM)



7 (20 μM)

10 **19**

According to Frederickson et al., compound **10** is a good inhibitor against all three type II dehydroquinase enzymes (p. 2613, l. 5-7). Therefore, active potential universal inhibitors must place that same structure into the active center of the enzyme. An enol intermediate is reported to be involved in a step in the enzymatic reaction of type II dehydroquinases. In summary, the art states the positive inhibition of type II dehydroquinases and the core structure of any potential universal inhibitor. Therefore, the problem set up by the state of the art is a need to provide effective and versatile inhibitors against type II dehydroquinases of the several organisms, showing more powerful inhibition than known compound 10; that is, compounds exhibiting $K_i < 200$ μM.

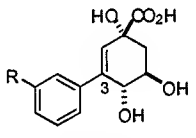
Applicants' strategy to develop new inhibitors of type II dehydroquinase was based on establishing extra binding interactions in the carbonyl binding pocket of these enzymes, where it is assumed that the enol intermediate is stabilized. Applicants have made more potent inhibitors than previously reported compound **10** by incorporating additional binding interactions into the core structure. Indeed, considering that type II dehydroquinase has two essential residues for enzyme activity, a tyrosine and an arginine, applicants have introduced groups that should establish π-stacking interactions with the tyrosine and also electrostatic interactions with the arginine.

It is known that π-stacking interactions are stronger between an electron-rich and an electron-withdrawing ring. As the tyrosine is an electron-rich aromatic group, applicants have introduced diverse electron-withdrawing groups as substituents in the ring of aromatic radicals on those potential inhibitors, in order to increase that effect. Therefore, the π-π type interaction is

turned to be the strongest one at the binding of the instant compounds with the enzyme. Other important residues such as Pro, Asn, Ile, Gly and Ala and Asr also play a role in the active site of type II dehydroquinases. These residues do favour the incorporation of external aliphatic groups, for which the binding affinity is increased.

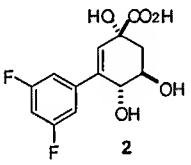
Based on this information, Applicants have provided an unexpected solution to the problem of inhibitors, substituted at least with an aliphatic chain or with an electron-withdrawn aromatic group as a radical, and able to place said radical within the active center of the enzyme. The compounds are those disclosed in new claim 19 and dependent claims thereon of the present application, which are new and result of a burden of research that is not suggested by the state of the art.

Examples of the inhibition constant, K_i, of some compounds according to the present disclosure are shown in the Table 1 below.

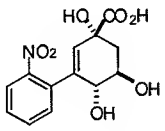


1

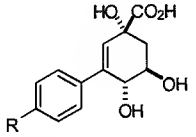
a R= H; **b** R= F;
c R= CF_3; **d** R= NO_2;
e R= OH; **f** R= CO_2H



2



3



4

a R= F; **b** R= CF_3;
c R= NO_2

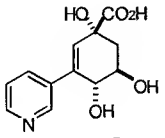


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Table 1. Inhibition results for compounds **1-4** against *M. tuberculosis* dehydroquinase.[a]

Compound	K_i (μ M) *M. tuberculosis*
1a	1.5
1b	1.5
1c	2.12
1d	**0.054**
1e	95
1f	150
2	2.44
4a	1.8
4b	17
4c	6.5
3	109
5	45

[a] K_M = 40μM at the assay conditions (50 mM Tris.HOAc, pH= 8.2, 25 °C)

Claim Rejections under 35 U.S.C. § 112

Claims 13 – 18 are finally rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Claims 13 – 18 have been canceled, without prejudice or disclaimer, and therefore the claim rejections under 35 U.S.C. § 112 are moot. Applicants respectfully request withdrawal of rejections under § 112, first paragraph.

Applicants have submitted new claims which do not contain "administering" a compound of the invention.

Claims 13 – 17 are finally rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for any biological or medical use of the compound.

Claims 13 – 17 have been canceled, without prejudice or disclaimer, and therefore the claim rejections under 35 U.S.C. § 112 are moot. Applicants respectfully request withdrawal of rejections under § 112, first paragraph.

Applicants have submitted new claims which exclude any biological or medical use of the compounds.

Claim Objections

Claims 3 and 5 are finally objected to under 37 C.F.R. 1.75(c) as being in improper form because claim 3 and claim 5 are multiply dependent upon other claims in a non-alternative way.

Claims 3 and 5 have been canceled, without prejudice or disclaimer, and therefore the claim objections under 37 C.F.R. 1.75(c) are moot. Additionally, none of the new claims added are multiply dependent. Applicants respectfully request withdrawal of the rejections under 37

C.F.R. 1.75(c).

Claim 2 and 4 are finally objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim.

Claims 2 and 4 have been canceled, without prejudice or disclaimer, and therefore the claim objections under 37 C.F.R. 1.75(c) are moot.

Conclusion

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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